

Painful Rash

Developed by

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Note to Instructors

This workbook is divided into five sections:

1. Introduction to the POPS System, introduction to and objectives of the clinical simulation, and a pretest
2. Color-coded booklets with pretest answers and the clinical problem
3. Group question and answer sheets
4. Posttest
5. Posttest answers

Each student should receive a copy of the introduction and pore-test to study and answer questions before the group problem-solving session.

Painful Rash

Pretest

Instructions: Please mark your answers to the following questions on this exam to facilitate later discussion and review. If your instructor has provided a separate answer form, please be sure to fill in the identification section; then answer the questions both on the form and on this exam.

Choose the *one* correct or most appropriate answer. If you do not know an answer, leave it blank. Do not guess. Health professionals who think they know something, but don't, can do real harm. Those who *know* they don't know something can get help.

Don't be upset if you don't know all the answers. The purpose of the pretest and objectives is to alert you to important concepts. The posttest will be similar to the pretest.

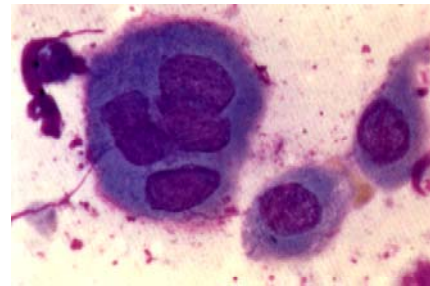
1. A previously healthy 32-year-old male is admitted with a tentative diagnosis of viral encephalitis. There is no history of exposure to mosquitoes in the last couple of weeks and there is no known outbreak of viral encephalitis in the community. A needle biopsy of the temporal lobe of the brain shows cells with intranuclear inclusion bodies. The most likely etiologic agent for this patient's encephalitis is:
 - A. A Flavivirus
 - B. A Herpes simplex virus
 - C. A Paramyxovirus
 - D. An Echovirus
 - E. The VZV virus
2. An 18-month-old baby girl presented to the emergency room with fever and a diffuse rash. Her temperature was 40°C, and her heart rate was 180/min. Physical examination shows a rash, more pronounced in the trunk, with both macular and vesicular lesions. Four vesicular lesions could be seen in the soft palate. The remainder of the physical examination was unremarkable. The chest X-ray is clear; CBC with differential showed a total WBC count of 9,000 with normal differential. This child most likely has:
 - A. Chickenpox
 - B. Herpangina
 - C. Measles
 - D. Roseola infantum
 - E. Scarlet fever
3. A 56-year-old woman under treatment for inoperable breast cancer develops the rash shown in the picture. Cytological examination of scrapings from the base of one of the vesicles reveals cells with intranuclear inclusions. The virus responsible for these lesions can be best described as a(n):
 - A. Enveloped, helical, DNA virus
 - B. Enveloped, helical, RNA virus
 - C. Enveloped, icosahedral, DNA virus
 - D. Naked, helical, RNA virus
 - E. Naked, icosahedral, DNA virus

4. A child presents with the lesions shown in the figure, similar lesions in the soles of the feet, and multiple vesicular eruptions on the hard palate. Which other of the listed diseases is most likely to be caused by the same strain of the involved infectious agent?
- A. Cervical carcinoma
 - B. Genital warts
 - C. Infantile diarrhea
 - D. Myocarditis
 - E. Pleurodynia



Questions 5 to 7 refer to the following case:

A 66-yr. old woman receiving chemotherapy for inoperable breast cancer develops a painful vesicular hemorrhagic rash in her right anterior chest. Cytological examination of scrapings from the base of one of the vesicles reveals the cells shown in the picture.



5. To confirm the diagnosis of this patient's disease you would prefer to:
- A. Ask for an HIV viral load
 - B. Culture the scrapings from the base of another vesicle
 - C. Order a special stain for Guarnieri bodies
 - D. Perform a direct immunofluorescence study on a smear of the base of a vesicle using enzyme-labeled VZV antibodies
 - E. Test the vesicular fluid for coxsackie virus antigens
6. In addition to the illustrated cytopathic effect, the virus responsible for these lesions may cause:
- A. B cell immortalization
 - B. Expression of T antigens on the infected cell membrane
 - C. Intracytoplasmic inclusion bodies
 - D. Intranuclear inclusion bodies
 - E. Rapid lysis of infected cells
7. The source of the etiological agent of this patient's disease is:
- A. Reactivation of a latent infection
 - B. Inhalation of contaminated secretion droplets
 - C. Transfusion of contaminated blood
 - D. Contact with an infected health care provider
 - E. Ingestion of contaminated food

8. Which of the following viruses reaches its target organ by hematogenous dissemination?
- A. Herpes simplex virus
 - B. Papilloma virus
 - C. Rhinovirus
 - D. Rotavirus
 - E. Rubella virus
9. Which of the following diseases is usually spread by respiratory secretions?
- A. ARDS associated with the Sin Nombre virus
 - B. Dengue
 - C. Measles
 - D. Viral encephalitis
 - E. Yellow fever
10. Which of the following diseases with cutaneous expression is caused by a virus that does NOT belong to the human herpes virus family?
- A. Chicken pox
 - B. Infectious mononucleosis
 - C. Kaposi's sarcoma
 - D. Molluscum contagiosum
 - E. Roseola infantum

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BOOK A

Note to Students: The fundamental purpose of all activities in the health-care professions is to help other people. Like all behaviors, helping behavior becomes more effective and natural with practice. This workbook enables you to practice by helping your fellow students to learn basic science. Your skill at helping your fellow students should relate to your ability to help your patients in the future. This is a *Patient-Oriented Problem-Solving ("POPS")* workbook designed for four students. Before beginning this session, you should have (a) studied the objectives designed to prepare you for it, (b) taken the pretest, and (c) reviewed the topics listed at the end of the pretest. Now, each of you should take one of the four color-coded booklets and follow the directions in it. If your group has only three students, one of you should take two booklets. Leave the remainder of the workbook intact until you are given further instructions.

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Introduction to the Patient-Oriented Problem-Solving (POPS) System

The purpose of this exercise is twofold. One is to help you learn how to apply your basic knowledge of immunology and microbiology to clinical problems. The other is to help you learn how to work with other people (i.e., how to learn from them and solve problems together). Good health professionals must first be able to learn from their patients and then be able to teach them. With this in mind, the data necessary for the solution of the patient-oriented problem have been divided into four parts so that everyone in your group must share data to arrive at a diagnosis.

This activity consists of four phases. First, you will review the attached set of objectives, do background reading on the topics to be covered, and complete the pretest on your own. In the second phase, you will join three other students and review the pretest answers in an "open-book" discussion. In the third phase, the group will solve patient-oriented problems. Finally, you will take a posttest, individually, which will enable you to assess your progress.

Please do your best to teach each other; seek additional information from your textbooks and share it with each other and, as a group; arrive at the correct diagnosis in a logical way. At the end of the exercise, everyone in the group should agree on the diagnosis and be able to identify the data that were (1) consistent with the diagnosis, (2) irrelevant to making the correct diagnosis or (3) inconsistent with the diagnosis. You also should understand the principles behind each observation and laboratory assay.

Painful rash

Introduction

This clinical simulation deals with viruses that cause vesicular eruptions, such as members of the Herpes virus family, Poxvirus family, and Coxsackie virus family. In the herpes family, the main viruses associated with vesicular eruptions are the Herpes simplex viruses that cause fever blisters (mainly type I) and genital herpes (mainly type 2), and the Varicella-Zoster virus (VZV), a DNA virus that causes chickenpox (varicella) in children and shingles (Zoster) in adults. In the poxvirus family, the main cause of disease with vesicular rash was the smallpox virus that was eradicated in the 1960's. In the coxsackie B family several serotypes can cause localized vesicular rash (herpangina, hand, foot-and-mouth disease. Amongst these viruses, Herpes simplex and VZV are unique in that they often become latent in sensory ganglia, and when reactivated tend to cause a painful eruption in the dermatome innervated by the infected ganglion. While reactivation of Herpes simplex may occur repeatedly, reactivation of the Zoster virus as shingles tends to occur only once, although in patients without adequate immunity reactivation of the Zoster virus may also be recurrent. This simulation will help you understand the different disease processes caused by herpes viruses, the diagnostic approaches used to confirm the diagnosis, and the available therapies.

When you have completed this activity you should be able to

- 1) list the different types of human herpesviruses and the diseases caused by each one.
- 2) compare and contrast the epidemiology and presentation of herpes, chickenpox, and shingles.
- 3) describe the different diagnostic approaches for infections caused by different human herpes viruses
- 4) describe the latent state of herpes viruses and the factors that may terminate such state.
- 5) discuss the immunoprophylaxis of chickenpox and other infections caused by members of the human herpes virus family.
- 7) describe the mode of action of anti-viral agents used in the treatment of infections caused by viruses of the herpes family.
- 8) select the appropriate therapy for a patient with shingles.

When you have become familiar with the objectives, complete the pretest on the next page.

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Pretest Correct Answers

Please discuss the answers to each question with the members of your group. Be sure that no one has any questions about them. If any one does, try to explain the rationale for the right answer. In explaining something to another person, most people gain a better understanding of it and often transmit a better understanding. *The pretest discussion and patient-oriented problem-solving parts of this activity are "open book."* Be sure to refer to textbooks, notes, and other written resources whenever questions arise.

1. The correct answer is B. The most frequent causes of viral encephalitis are included in the five possible answers to this question. The epidemiological data does not show the involvement of Echoviruses or Flaviviruses, likely to emerge as outbreaks due to either fecal-oral transmission (Echoviruses) or to transmission through arthropod bites (Flavivirus). The finding of cells with intranuclear inclusion bodies in the brain biopsy, on the other hand, is highly suggestive of the involvement of a DNA virus. Of the viruses listed as possible etiological agents, only Herpes Simplex and VZV are DNA virus. However, VZV usually causes post-infectious encephalitis, a very unlikely scenario in a 32 yr. old male without recent history of rash and Herpes encephalitis is considerably more frequent than post-infectious VZV encephalitis.
4. The correct answer is C. The clinical picture is that of hand-foot-and mouth disease, caused by Coxsackie A viruses of many different serotypes. Of the diseases listed as possibly associated with the same virus, infantile diarrhea is not commonly associated with Coxsackie A viruses. Coxsackie B viruses usually cause viral myocarditis and pleurodynia. Papilloma viruses cause cervical carcinoma and genital warts.
8. The correct answer is E. With the exception of Herpes simplex and VZV viruses that reach the skin through retrograde diffusion through nerve roots, all rash-causing viruses reach the skin through viremia. Of those viruses listed as possible choices, only Herpes simplex (discussed above) and Rubella virus cause skin rashes. Papilloma viruses cause skin and mucosal warts, rhinoviruses are agents of the common cold, and rotaviruses cause infantile diarrhea.

After discussing all the pretest answers, please instruct your group to proceed to the "Introduction to the Clinical Problem."

Painful rash

Introduction to the Clinical Problem

The purpose of this exercise is to allow you to apply your knowledge of the disease etiology, diagnosis and management of patients with vesicular rash caused by a viral infection.

Each of the four group members has a different part of a clinical scenario. Each student starts by presenting his data to the group. After reading the given information you will find several question. Try to answer each question as a group, based on the interpretation of the presented information and on resources that you have brought to the meeting. If several opinions emerge about the questions, each member of the group should be ready to defend his or her position, backing it up with data from the available sources. After discussion of the first set of data is completed, compare your answers with those on the correct answer sheet.

This process will then be repeated for the other three parts of this clinical case.

Begin the problem by presenting the **patient's history on the following page to your colleagues.**

Painful rash

Ms. Alice Helms

A general surgery resident has called the dermatology clinic and asked for immediate consultation on Alice Helms, a 72 year old woman who had undergone a left mastectomy four days earlier and has returned to surgery clinic for a dressing change.

Mrs. Helms had an uneventful immediate post-operative recovery and was discharged from the hospital two days following surgery wearing a circumferential elastic bandage around the chest. She reported that at the time of discharge she was experiencing mild itching around the chest.

Within 24 hours she noted red patches and increasing pain on the left side of the chest, extending from the site of the surgical incision where a drain remained in place, around the trunk to the left side of the back. By the time of her return to surgery clinic, the pain was severe.

Mrs. Helms' dermatologic history is significant for previous episodes of poison ivy. She can recall no other rashes except for the usual childhood illnesses including measles and chicken pox. She has allergic rhinitis each spring during pollen season.

Answer the following:

What is the most likely diagnosis?

What is the source of Mrs. Helms problem?

Did the recent surgery have anything to do with Mrs. Helms' rash?

What is indicated by the change in symptoms from pruritus to pain?

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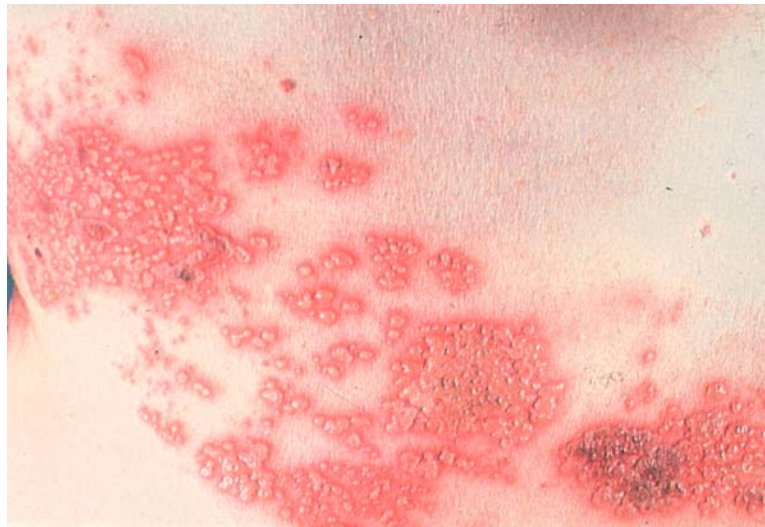
Physical examination

Vital Signs: Temp 38°C
 Pulse 92/min
 Respirations 24/min and shallow
 BP 160/94 mmHg

General Appearance: A somewhat disheveled elderly woman.

On the left side of the chest was an intact suture line with a vacuum drain in place at the lateral tip of the wound. Sero-sanguinous drainage was noted. There were discrete, mildly edematous and erythematous plaques above and below the suture line, extending around the chest from the sternum to the vertebral column, only on the left side. Within each plaque there were multiple vesicles (see figure).

Remainder of the physical exam was noncontributory.



Answer the following:

Do findings on physical exam change your diagnosis?

Explain the significance of the linear distribution of the skin lesions.

What laboratory testing may be done to confirm your diagnosis?

(After answering these questions proceed to book 2)

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BOOK B

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2. The correct answer is A. of the conditions listed as choices, only chickenpox and herpangina are associated with vesicular rashes, but the vesicular rash of herpangina is limited to the oral mucosa. On the other hand, the centripetal nature of the rash and the simultaneous presence of lesions in different stages of evolution are typical of chickenpox. Scarlet fever is associated with an erythematous rash, measles and roseola infantum are associated with maculopapular (morbilliform) rashes, which in the case of roseola infantum is not too obvious and usually only detected as the child becomes afebrile.
10. The correct answer is D. Molluscum contagiosum is caused by a poxvirus, while all the other conditions listed are caused by viruses of the human herpes group (A-VZV, B-Epstein-Barr virus, C-HHV-8, and E-HHV-6 and 7).

After discussing all the pretest answers, please instruct your group to proceed to the "Introduction to the Clinical Problem."

Painful rash

Introduction to the Clinical Problem

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Each of the four group members has a different part of a clinical scenario. Each student starts by presenting his data to the group. After reading the given information you will find several question. Try to answer each question as a group, based on the interpretation of the presented information and on resources that you have brought to the meeting. If several opinions emerge about the questions, each member of the group should be ready to defend his/her position, backing it up with data from the available sources. After discussion of the first set of data is completed, compare your answers with those on the correct answer sheet.

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Discussion (part 1)

Mrs. Helms developed a painful vesicular rash with dermatomal distribution in her post-operative period after a left mastectomy. The characteristics of the rash are suggestive of herpes Zoster (shingles). Your differential should include contact dermatitis caused by the elastic bandage and bacterial wound infection. Herpes Zoster is the clinical manifestation of the reactivation of dormant VZV from the dorsal root ganglion. Mrs. Helms acquired VZV in childhood (she had a history of chickenpox) and the reactivation may be related to waning immunity associated with aging, perhaps in combination with depressed cell-mediated immunity, commonly observed in the post-operative period as a consequence of a variety of factors, including

- (A) posttraumatic activation of inflammatory cells that release PGE₂, known to depress T lymphocyte and accessory cell functions
- (B) general anesthesia and administration of painkillers, known to depress NK cell functions

Additionally, tissue injury (in this case associated to the surgical procedure) is often followed by herpetic recurrences. This may be secondary to a decrease in nerve growth factor (NGF) that is believed to control viral latency in neurons. In cultures of latently infected neural cells, NGF deprivation will result in rapid expression of the virus.

Many patients report tingling or itching preceding the development of the herpetic eruption. As the rash develops, pain replaces the itching sensation. This evolution likely reflects the progressive inflammatory reaction caused by viral replication and propagation along the sensory nerves converging to the dorsal root from which the virus becomes reactivated. The linear distribution of the vesicular rash reflects the area of the skin (dermatome) with innervation from the infected dorsal root.

A combination of clinical findings and the finding of typical cytopathogenic effect (CPE) on cells of a smear from the base of a vesicle (Tzanck preparation) is usually considered sufficient for diagnosis. However, screening laboratory tests and skin biopsy may also help establish the diagnosis.

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Ms. Alice Helms (continued)

LABORATORY RESULTS

CBC WITH DIFFERENTIAL (NORMAL VALUES)

Hemoglobin	12.6 g/dL	(12-16 g/dL)
White blood cells	10.2 x 10 ³ /mL	(4.8-10.8 x 10 ³ /mL)
Neutrophils	42%	(50-75%)
Lymphocytes	51%	(20-45%)
Eosinophils	2%	(0-5%)
Basophils	1%	(0-2%)
Monocytes	4%	(0-10%)

SERUM CHEMISTRY PROFILE

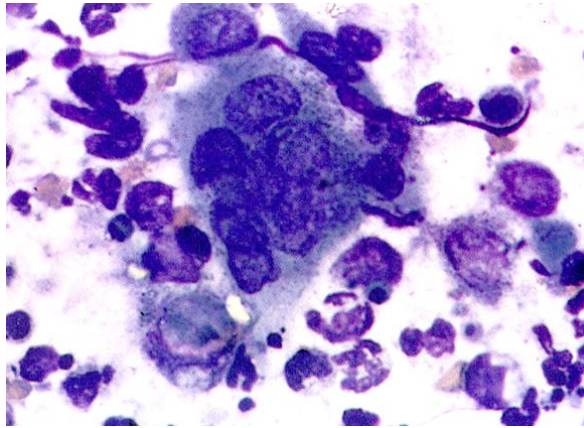
Sodium	139 mmol/L	(137-145 mmol/L)
Potassium	4.7 mmol/L	(3.6-5.0 mmol/L)
Chloride	101 mmol/L	(98-107 mmol/L)
Calcium	9.5 mg/dL	(8.4-10.2 mg/dL)
Glucose	88 mg/dL	(65-105 mg/dL)
Blood urea nitrogen	15 mg/dL	(7-17 mg/dL)
Creatinine	1.3 mg/dL	(0.7-1.2 mg/dL)
Total protein	7.1 gm/dL	(6.3-8.2 gm/dL)
Lactate dehydrogenase	150 IU/L	(313-618 IU/L)
Alkaline phosphatase	99 IU/L	(38-126 IU/L)
Uric acid	5.1 mg/dL	(2.5-7.5 mg/dL)
Cholesterol	175 mg/dL	(100-200 mg/dL)

URINALYSIS

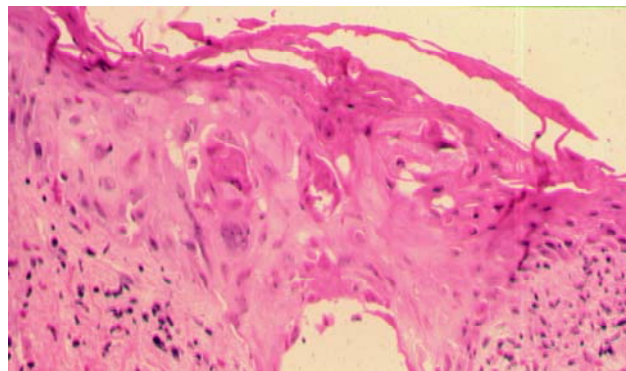
pH	6.5	(5-7)
Specific gravity	1.021	(1.003-1.030)
Glucose	negative	(negative)
Ketones	negative	(negative)
Protein	negative	(negative)
Bilirubin	negative	(negative)
Blood	negative	(negative)
Nitrite	negative	(negative)
White blood cells	0-1	(0-4)
Red blood cells	0-2	(0-2)

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Tzanck preparation obtained from the base of a skin vesicle



Photomicrographs of a **skin biopsy** from a lesion on the left side of the chest



Answer the following:

What is the significance of the increased lymphocyte count on the differential?

How do you interpret the Tzanck preparation?

How do you interpret the skin biopsy?

How will you treat this patient? What is (are) the mechanism(s) of action of the indicated antimicrobial(s)?

(After answering these questions move to book 3)

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5. D is the correct answer. The clinical presentation is suggestive of Zoster (Shingles). To confirm the diagnosis is necessary to obtain unquestionable evidence for the presence of VZV in the lesions, and that can be obtained by direct immunofluorescence. Culture of the scrapings from the basis of another vesicle could also be confirmatory, but it takes longer. Guarnieri bodies are associated with poxvirus infections. Coxsackie viruses and HIV do not cause the type of rash described for this patient.
6. The correct answer is D. VZV, like all members of the Human Herpes group, replicates in the nucleus and, therefore, replication can be associated with intranuclear inclusion bodies. The other CPE effect seen in cells infected with VZV virus is the formation of multinucleated giant cells. The Epstein-Barr virus, another member of the human herpes group, can cause B cell immortalization. The expression of T antigens on the membrane of infected cells is characteristic of polyoma viruses. Intracytoplasmic inclusion bodies can be seen in cells infected with pox viruses or several RNA viruses, all of them replicating in the cytoplasm. Cell lysis is caused by a variety of virus, usually naked (e.g., picornavirus)
7. The correct answer is A. The primary infection with VZV is usually acquired in childhood and presents as chickenpox. The virus then may remain latent in the dorsal ganglia for long periods of time, and may reactivate under favorable circumstances, causing shingles. Chickenpox may be acquired by direct contact with an infected patient, but is most frequently transmitted by inhalation of contaminated secretion droplets.

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Introduction to the Clinical Problem

The purpose of this exercise is to allow you to apply your knowledge of the disease etiology, diagnosis and management of patients with vesicular rash caused by a viral infection.

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Discussion (2)

Viral infections usually elicit absolute increases in the peripheral blood lymphocyte count because of the mobilization of T lymphocytes as part of the anti-viral immune response.

The Tzanck preparation showed multinucleated giant cells, one of the typical cytopathogenic effects of VZV (the other being intranuclear inclusion bodies). However, these morphological changes are not unique for VZV as Herpes simplex viruses cause identical changes. Therefore, to confirm the identity of the virus one needs to either use direct immunofluorescence with antibodies specific for the different viruses, or PCR to identify unique genomic sequences for each one of them.

The skin biopsy shows prominent acantholysis and intra-epidermal vesicle formation. Ballooning degeneration of epidermal cells is noted. Eosinophilic inclusion bodies are seen in the balloon cells. In the dermis there is edema and a moderately severe inflammatory infiltrate of mononuclear cells. Vasculitis is noted with neutrophils within and around vascular walls. These changes are typical of herpes-Zoster infection.

Infections caused by VZV can be treated with acyclovir, famcyclovir, and valacyclovir (the last two drugs being easier to administer due to improved pharmacokinetics over acyclovir). All these drugs are nucleoside analogues, inactive until phosphorylated by a viral thymidine kinase. After the initial phosphorylation cellular or viral kinases add additional phosphate groups. In their active form these compounds have anti-viral effects via two mechanisms: they are incorporated into nascent viral DNA and cause premature chain termination, and they bind irreversibly to the viral DNA polymerase. However, the affinity of these compounds for the DNA polymerase of VZV is lower than the affinity for the DNA polymerase of herpes simplex viruses and, therefore, higher doses are required in the treatment of infections caused by VZV.

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Ms. Alice Helms (continued)

A chest X-ray was ordered and Mrs. Helms was started on valacyclovir 1 g tid for 7 days. At the end of that time she returned for follow up. Blisters had resolved. There remained mild erythema and hyperpigmentation at the site of the eruption on the left side of the trunk. She continued to complain of pain though it was decreased in intensity.

Answer the following:

Why was a chest X-ray obtained?

Why did Mrs. Helms continue to have pain after the skin lesions had resolved?

Is Mrs. Helms likely to have another episode of herpes Zoster in the future?

Painful rash

Discussion (3)

In immunocompromised patients VZV may disseminate and infect the lungs, brain and liver. Although Mrs. Helms was not severely immunocompromised, her Zoster may have been related to a depression of her cell-mediated immunity and checking the lungs and liver enzymes would be advisable. The chest X-ray, if normal, would still be valuable, because it would provide a baseline image to compare with future films, if Mrs. Helms started to present symptoms suggestive of lung involvement. VZV pneumonia is a form of interstitial pneumonia, often difficult to diagnose in the early stages. Comparing two films obtained at different points of time is very valuable in this context.

Up to 30% of patients (particularly in the age group over 65 yr.) suffering from VZV develop a chronic pain syndrome known as postherpetic neuralgia that may last weeks or months. The pathogenesis of this syndrome is not fully understood but it may reflect the slowness of the healing process of affected sensory nerves.

At one time it was said that varicella and herpes Zoster never recurred, but this is not necessarily true if the patients are immunocompromised and fail to maintain protective immunity or if they are genetically unable to respond to VZV antigens. The likelihood of recurrence is small, but cannot be ruled out.

Painful Rash

Developed by

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BOOK D

Note to Students: The fundamental purpose of all activities in the health-care professions is to help other people. Like all behaviors, helping behavior becomes more effective and natural with practice. This workbook enables you to practice by helping your fellow students to learn basic science. Your skill at helping your fellow students should relate to your ability to help your patients in the future. This is a *Patient-Oriented Problem-Solving ("POPS")* workbook designed for four students. Before beginning this session, you should have (a) studied the objectives designed to prepare you for it, (b) taken the pretest, and (c) reviewed the topics listed at the end of the pretest. Now, each of you should take one of the four color-coded booklets and follow the directions in it. If your group has only three students, one of you should take two booklets. Leave the remainder of the workbook intact until you are given further instructions.

Painful rash

Introduction to the Patient-Oriented Problem-Solving (POPS) System

The purpose of this exercise is twofold. One is to help you learn how to apply your basic knowledge of immunology and microbiology to clinical problems. The other is to help you learn how to work with other people (i.e., how to learn from them and solve problems together). Good health professionals must first be able to learn from their patients and then be able to teach them. With this in mind, the data necessary for the solution of the patient-oriented problem have been divided into four parts so that everyone in your group must share data to arrive at a diagnosis.

This activity consists of four phases. First, you will review the attached set of objectives, do background reading on the topics to be covered, and complete the pretest on your own. In the second phase, you will join three other students and review the pretest answers in an "open-book" discussion. In the third phase, the group will solve patient-oriented problems. Finally, you will take a posttest, individually, which will enable you to assess your progress.

Please do your best to teach each other; seek additional information from your textbooks and share it with each other and, as a group, arrive at the correct diagnosis in a logical way. At the end of the exercise, everyone in the group should agree on the diagnosis and be able to identify the data that were (1) consistent with the diagnosis, (2) irrelevant to making the correct diagnosis, or (3) inconsistent with the diagnosis. You also should understand the principles behind each observation and laboratory assay.

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Pretest Correct Answers

Please discuss the answers to each question with the members of your group. Be sure that no one has any questions about them. If any one does, try to explain the rationale for the right answer. In explaining something to another person, most people gain a better understanding of it and often transmit a better understanding. *The pretest discussion and patient-oriented problem-solving parts of this activity are "open book."* Be sure to refer to textbooks, notes, and other written resources whenever questions arise.

3. The correct answer is C. the clinical history and presentation are characteristic of Zoster (shingles), caused by the Varicella-Zoster virus (VZV). The VZV is an enveloped, icosahedral virus with DNA genome (as all other members of the human herpes group).
9. The correct answer is C. Measles is transmitted through inhalation of aerosolized infected secretions exhaled when an infected patient coughs. Dengue, Viral encephalitis and Yellow fever are transmitted by mosquito bites. The Sin Nombre virus is transmitted by contact with infected rodent excreta.

Painful rash

Introduction to the Clinical Problem

The purpose of this exercise is to allow you to apply your knowledge of the disease etiology, diagnosis and management of patients with vesicular rash caused by a viral infection.

Each of the four group members has a different part of a clinical scenario. Each student starts by presenting his data to the group. After reading the given information you will find several question. Try to answer each question as a group, based on the interpretation of the presented information and on resources that you have brought to the meeting. If several opinions emerge about the questions, each member of the group should be ready to defend his/her position, backing it up with data from the available sources. After discussion of the first set of data is completed, compare your answers with those on the correct answer sheet.

Painful Rash

Mrs. Helms Grandson

Carter, Mrs. Helms two year old grandson, fell ill about two weeks after Mrs. Helms came down with herpes Zoster. Carter's mother noticed that the child become irritable and on taking his temperature found that he was febrile (102.5°F). When she gave him a bath that evening she noted some pimples on the anterior aspect of the thorax. She gave him Tylenol and he slept normally. When Carter awoke the next morning she noted that he now had a more prominent rash over the trunk, consisting of pink spots, tiny blisters and pustules, and a few crusted lesions. The rash continued to spread, and eventually some lesions appeared on the limbs and face (see the figure below). Carter attends kindergarten, is current on his immunizations, is well developed for age, and has been a healthy child. He had visited his grandmother when she was sick.



Answer the following:

Which infectious agents could have caused Carter's rash?

What is your diagnosis?

What is the most likely source of Carter's infection?

Is Carter's infection contagious?

How could this disease be prevented?

What vaccinations should Carter have received?

Does the vaccination history change your diagnosis?

What therapy is indicated for Carter?

Painful rash

Discussion (4)

Viral agents usually cause vesicular rashes. Herpes simplex, VZV, smallpox, and coxsackie A viruses would come to mind as possibilities, although smallpox could be immediately ruled out because it is an extinct disease.

The distribution of the rash, affecting predominantly the trunk (centrifugal rash), its vesicular nature, and the fact that there are lesions in several stages of evolution (different "crops") suggests varicella (chickenpox) as the most likely diagnosis. Coxsackie A viruses usually cause a less diffuse eruption affecting the mucosa and/or extremities. Smallpox classically presented with a single "crop" of lesions, all at the same stage of evolution.

Carter could have been infected at the kindergarten or by close contact with his grandmother. The last hypothesis would be in agreement with the two-week incubation period of chickenpox.

VZV is highly contagious. The rate of infection is as high as 90% of non-immunized close contacts. The disease can be spread by the respiratory route and by direct contact with skin vesicles. Patients are contagious before and during symptoms, until the rash has healed.

Chickenpox is effectively prevented by immunization with an attenuated vaccine. A two-year-old child like Carter should have received the following vaccines (shaded area):

Vaccine	Birth	1 mo.	2 mo.	4 mo.	6 mo.	12 mo.	15 mo.	18 mo.	4-6 yr.	11-12	14-16
Hepatitis B	Dose 1										
		Dose 2			Dose 3						
DTaP *			Dose 1	Dose 2	Dose 3		DTaP		DTaP		Td booster
Hib [¶]			Dose 1	Dose 2	Dose 3						
Polio [¥]			Dose 1	Dose 2		Dose 3			Booster		
						Dose 1			Booster		
VZV ^{††}						Dose 1					

¹ Recommendations approved by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics and the American Academy of Family Physicians (Modified from Pediatrics, 105: 148, 2000).

* DTaP = Diphtheria, tetanus, and acellular pertussis

[¶] *Haemophilus influenzae* type b PRP-conjugate vaccine

[¥] Inactivated polio vaccine is recommended for routine vaccination in the U.S.

[§] Third dose not needed if PRP-OMP is used

** MMR= measles, mumps, rubella

^{††} Varicella-zoster virus vaccine

No vaccination is 100% effective. As a rule, 1 to 5% of normal children will not respond to one or another immunization. This is not relevant from the point of view of transmission of the disease, because for most diseases a rate of immunization in the general population over 60% will effectively prevent transmission. because the VZV vaccine is now widely used the likelihood that he may have contracted the disease in his kindergarten is very small; most likely he contracted the disease when he visited with his sick grandmother.

Because Carter is a healthy child, one would expect complete recovery. However, because he may be a non-responder to VZV, therapy with famcyclovir or valacyclovir may be indicated.

Painful rash

Summary

Mrs. Helms developed a painful vesicular rash with dermatomal distribution in her post-operative period after a left mastectomy. The characteristics of the rash were suggestive of herpes Zoster (shingles). The differential should include contact dermatitis caused by the elastic bandage and bacterial wound infection. Herpes Zoster is the clinical manifestation of the reactivation of dormant VZV from the dorsal root ganglion. Mrs. Helms acquired VZV in childhood (she had a history of chickenpox) and the reactivation may be related to waning immunity associated with aging, perhaps in combination with depressed cell-mediated immunity, commonly observed in the post-operative period as a consequence of a variety of factors, including

- (A) posttraumatic activation of inflammatory cells that release PGE₂, known to depress T lymphocyte and accessory cell functions
- (B) general anesthesia and administration of painkillers, known to depress NK cell functions

Additionally, tissue injury (in this case associated to the surgical procedure) is often followed by herpetic recurrences. This may be secondary to a decrease in nerve growth factor (NGF) that is believed to control viral latency in neurons. In cultures of latently infected neural cells, NGF deprivation will result in rapid expression of the virus.

Many patients report tingling or itching preceding the development of the herpetic eruption. As the rash develops, pain replaces the itching sensation. This evolution likely reflects the progressive inflammatory reaction caused by viral replication and propagation along the sensory nerves converging to the dorsal root from which the virus becomes reactivated. The linear distribution of the vesicular rash reflects the area of the skin (dermatome) with innervation from the infected dorsal root.

A combination of clinical findings and the finding of typical CPE on skin scrapings (Tzanck preparation) is usually considered sufficient for diagnosis of shingles. The Tzanck preparation from Mrs. Helms showed multinucleated giant cells, one of the typical cytopathogenic effects of VZV (the other being intranuclear inclusion bodies). However, these morphological changes are not unique for VZV, herpes simplex viruses cause identical changes. Therefore, to confirm the identity of the virus it may be necessary to either use direct immunofluorescence with antibodies specific for the different viruses, or PCR to identify unique genomic sequences for each one of them.

A skin biopsy of Mrs. Helms' rash showed changes typical of Herpes Zoster - prominent acantholysis and intra-epidermal vesicle formation, ballooning degeneration of epidermal cells, eosinophilic inclusion bodies in the balloon cells. In the dermis there was edema and a moderately severe inflammatory infiltrate of mononuclear cells. Vasculitis was noted with neutrophils within and around vascular walls.

Infections caused by VZV can be treated with acyclovir, famcyclovir, and valacyclovir (the last two drugs being easier to administer due to improved pharmacokinetics over acyclovir). All these drugs are nucleoside analogues, inactive until phosphorylated by a viral thymidine kinase.

After the initial phosphorylation cellular or viral kinases add additional phosphate groups. In their active form these compounds have anti-viral effects via two mechanisms: they are incorporated into nascent viral DNA and cause premature chain termination, and they bind irreversibly to the viral DNA polymerase. However, the affinity of these compounds for the DNA polymerase of VZV is lower than the affinity for the DNA polymerase of herpes simplex viruses and, therefore, higher doses are required in the treatment of infections caused by VZV.

In immunocompromised patients VZV may disseminate and infect the lungs, brain and liver. Although Mrs. Helms was not severely immunocompromised, her Herpes Zoster may have been related to a depression of her cell-mediated immunity and checking the lungs and liver enzymes would be advisable. The chest X-ray, if normal, would still be valuable, because it would provide a baseline image to compare with future films, if Mrs. Helms started to present symptoms suggestive of lung involvement. VZV pneumonia is a form of interstitial pneumonia, often difficult to diagnose in the early stages. Comparing two films obtained at different points of time is very valuable in this context.

Up to 30% of patients (particularly in the age group over 65 yr.) suffering from VZV develop a chronic pain syndrome known as postherpetic neuralgia that may last weeks or months. The pathogenesis of this syndrome is not fully understood but it may reflect the slowness of the healing process of affected sensory nerves.

At one time it was said that varicella and herpes Zoster never recurred, but this is not necessarily true if the patients are immunocompromised and fail to maintain protective immunity or if they are genetically unable to respond to VZV antigens. The likelihood of recurrence is small, but cannot be ruled out.

Mrs. Helms, grandson, Carter, developed a febrile disease with vesicular rash about two weeks after Mrs. Helms became ill. Viral agents usually cause vesicular rashes. Herpes simplex, VZV, smallpox, and coxsackie A viruses would come to mind as possibilities, although smallpox could be immediately ruled out because it is an extinct disease.

The distribution of the rash, affecting predominantly the trunk (centrifugal rash), its vesicular nature, and the fact that there are lesions in several stages of evolution (different "crops") suggests varicella (chickenpox) as the most likely diagnosis. Coxsackie A viruses usually cause a less diffuse eruption affecting the mucosa and/or extremities. Smallpox classically presented with a single "crop" of lesions, all at the same stage of evolution.

VZV is highly contagious. The rate of infection is as high as 90% of non-immunized close contacts. The disease can be spread by the respiratory route and by direct contact with skin vesicles. Patients are contagious before and during symptoms, until the rash has healed. Carter could have been infected at the kindergarten or by close contact with his grandmother. The last hypothesis would be in agreement with the two-week incubation period of chickenpox.

Chickenpox is effectively prevented by immunization with an attenuated vaccine. A two-year-old child like Carter should have received the following vaccines (shaded area):

Painful rash

Summary (ctd.)

Vaccine	Birth	1 mo.	2 mo.	4 mo.	6 mo.	12 mo.	15 mo.	18 mo.	4-6 yr.	11-12	14-16
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DTaP *			Dose 1	Dose 2	Dose 3		DTaP		DTaP		Td booster
Hib¶			Dose 1	Dose 2	Dose 3						
Polio¥			Dose 1	Dose 2		Dose 3			Booster		
						Dose 1			Booster		
VZV††						Dose 1					

¹ Recommendations approved by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics and the American Academy of Family Physicians (Modified from Pediatrics, 105: 148, 2000).

* DTaP = Diphtheria, tetanus, and acellular pertussis

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Posttest

Select the best answer for each question. Please mark your answers on this exam to facilitate discussion and later review. If your instructor has provided a separate answer form, be sure you identify yourself on the form, then begin your answers with question 1. Mark your answers both on the form and on this exam. Only one answer is correct.

1. A 32-year old male is admitted with a tentative diagnosis of viral encephalitis. There is no history of exposure to mosquitoes in the last couple of weeks and there is no known outbreak of viral encephalitis in the community. A needle biopsy of the frontal lobe of the brain is inconclusive. An MRI of the brain is compatible with viral encephalitis. The most important intervention in this patient is to:
 - A. Keep the patient in the hospital for a few more days under close observation
 - B. Order serologies for the most common agents of viral encephalitis
 - C. Perform a spinal tap and send CSF for direct examination and PCR
 - D. Start a third generation cephalosporin IV immediately
 - E. Start treatment with acyclovir immediately

Questions 2 to 3 refer to the following case:

A sexually active 22-year-old male presents to the STD clinic with the lesions shown in the picture. A scraping of the base of one of the vesicles shows multinucleated giant cells. He explains that he had a similar eruption in the same area two months earlier.



2. The recurrent nature of this patient's lesions is a consequence of:
 - A. A second infection with a similar virus with a different serotype
 - B. Lack of effective protection by the immune response
 - C. Rapid development of resistance to anti-viral agents
 - D. Repeated reactivation of a latent infection in a sensory ganglia
 - E. Variation of the antigenic make-up of the causative agent
3. The best preventive measure to avoid transmission of this disease to this patient's sexual partners is:
 - A. Application of topical famcyclovir prior to intercourse
 - B. Immunization of all non-infected contacts
 - C. Prophylactic administration of acyclovir to the patient and his partner(s)
 - D. Treatment of all lesions with interferon- α
 - E. Use of barrier contraceptives

Questions 4 and 5 refer to the following clinical case:

A child presents with multiple vesicular eruptions on the mucous membranes of the mouth which resolve spontaneously within three weeks. However, during the next twelve months, the child suffers several recurrent infections, characterized by blisters in the epidermo-mucosal junction of the peri-oral region. In all cases there is complete spontaneous recovery followed by symptom-free intervals.

4. Which of the following drugs is most likely to be useful to alleviate this child's symptoms?
 - A. A blocker of protein synthesis
 - B. A reverse transcriptase inhibitor
 - C. A viral protease inhibitor
 - D. An activator of cellular ribonucleases
 - E. An inhibitor of viral DNA synthesis
5. The low toxicity of the anti-viral agents used to treat this infection is a consequence of the fact that these drugs:
 - A. block a viral enzyme which has no homologue in human cells
 - B. block specifically the penetration and uncoating of the viral nucleic acid
 - C. inhibit the activity of a viral protease which processes viral proteins but lack any effect on human proteins
 - D. only become active after a series of phosphorylations initiated by a viral thymidine kinase
 - E. penetrate non-infected cells very poorly

Questions 6 and 7 refer to the following case:

A 5-yr. old girl presents with fever (103°F) and a rash that started in the trunk and has spread to the face. Physical examination shows maculopapular, vesicular, pustular, and crusted lesions in several areas of the body.

6. This child has most likely an infection caused by:
 - A. Coxsackie A virus
 - B. Herpes simplex virus
 - C. Measles virus
 - D. *Streptococcus pyogenes*
 - E. Varicella-Zoster virus
7. This girl has a 2-yr-old sister that became ill with a similar disease four weeks after she was sick and an older brother that has remained healthy. The older brother attends public school, the older sister attends pre-school at her brother's school, and the younger sister stays at a private kinder garden. What would be the most likely source of infection for the young sister?
 - A. Her brother
 - B. Her mother
 - C. Her older sister
 - D. Other children attending the kinder garden

8. The mother of an 18-month old girl seeks medical attention because her daughter is febrile, restless, and refuses food. Physical examination is unremarkable except for the fact that several small vesicular lesions, some ulcerated, are seen in the tonsils and posterior pharynx. The agent most likely to cause this disease is a:
- A. (+)RNA enterovirus
 - B. (-)RNA paramyxovirus
 - C. dsDNA herpes virus
 - D. dsDNA poxvirus
 - E. ssDNA parvovirus
9. The best treatment for this child's disease is:
- A. Famcyclovir
 - B. Hyperimmune gamma globulin
 - C. Interferon- α
 - D. Ribavirin
 - E. Supportive
10. Which of the following viruses reaches its target organ by hematogenous dissemination?
- A. Coxsackie B viruses
 - B. Herpes simplex virus
 - C. Norwalk virus
 - D. Rabies virus
 - E. Rhinovirus

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Posttest Correct Answers

DO NOT LOOK AT THEM OR REMOVE THEM UNTIL YOU HAVE COMPLETED THE POSTTEST.

Discuss the answers with each other to be sure none of you have any misconceptions!

1. The correct answer is E. Of all the common agents of viral encephalitis, HSV-1 and 2 are the only ones that can be effectively treated with anti-viral agents (acyclovir and related compounds). Hence, while B and C are important steps for diagnostic confirmation, and hospitalization is indicated in a patient with encephalitis, it is most important to start treatment, in order to reduce morbidity and mortality. Administration of anti-bacterial agents, on the other hand, is hardly indicated, because viruses are the usual etiologic agents of infectious encephalitis.
2. The correct answer is D. HSV and VZV viruses tend to remain latent in sensory ganglia and cause vesicular rashes when reactivated. Although immunocompromised patients may be more susceptible to reactivation and more extensive disease, in most patients the recurrences are not associated with an obvious immune deficit. Resistance to acyclovir is rare, and the resistant strains are usually less pathogenic than the ones not resistant. Antigenic variation has not been reported with these viruses, which are not likely to cause re-infections because of their very limited serological diversity.
3. The correct answer is E. When lesions are obvious, sexual intercourse should be avoided altogether. However, transmission is possible without obvious lesions, and the routine use of barrier contraceptives should be strongly recommended to patients known to have herpes genitalis, even when the lesions are not detectable.
4. The correct answer is E. This is a typical description of recurrent herpes simplex. The drugs of choice for herpes simplex (acyclovir and related compounds) block viral DNA synthesis. Protein synthesis inhibition is not an effective strategy for anti-viral therapy because viral proteins are synthesized by the host ribosomes, and the drugs would inhibit both viral and host protein synthesis, therefore with high degree of toxicity. RT is unique to retroviruses and hepadnaviruses. Viral proteases play a critical role in the replication of (+)RNA viruses. Activation of cellular ribonucleases would have adverse effects to the cell and cause toxic side effects..
5. The correct answer is D. Acyclovir and related compounds are administered in an inactive form that needs to be phosphorylated in order to block DNA synthesis. The initial phosphorylation requires a viral thymidine kinase, and therefore, the drug is only activated in infected cells and the toxicity is minimal.
6. The correct answer is E. The rash described in this patient is typical of chickenpox - predominance in the trunk and lesions in various stages of development (crops). Chickenpox is caused by VZV. Coxsackie virus and Herpes simplex viruses can also cause vesicular rashes, but their distribution is totally different. The morbilliform rash of measles is the prototype for maculopapular rashes. *Streptococcus pyogenes* causes scarlet fever by releasing erythrogenic toxin that causes generalized skin erythema, not easily confused with a vesicular rash.

7. The correct answer is D. The incubation period for chickenpox is usually of about two weeks, maximum three. The possibility that the virus was transmitted to the brother, who remained asymptomatic, and from him to the younger sister, cannot be completely ruled out but is highly unlikely
8. The correct answer is A. The clinical diagnosis in this case would be herpangina, caused by one of the coxsackie A viruses, which are (+)RNA enteroviruses of the picornavirus group.
9. The correct answer is E. There is no known antiviral agent effective against coxsackie viruses, and herpangina follows a benign course.
10. The correct answer is A. Coxsackie B viruses are enteroviruses that cause disease in various target organs (e.g., heart) that are reached by hematogenous dissemination. Norwalk virus is acquired by ingestion and causes disease in the GI tract. Rabies virus and HSV virus reach their target organs through nervous tissue. Rhinoviruses are acquired by inhalation and cause infection of the upper respiratory tract.

When your group has finished reviewing the posttest, you have completed the activity. Have you achieved the objectives listed in the Introduction? Some of you may wish to discuss your reactions to this Patient-Oriented Problem-Solving session with your instructor.

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Color plate

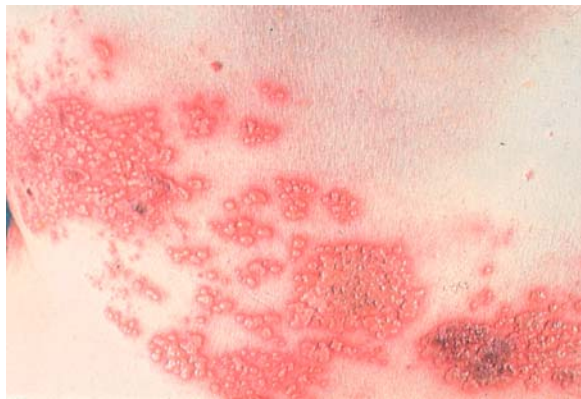


Figure 1

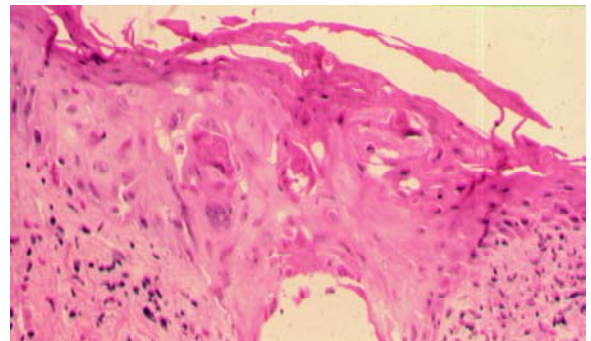


Figure 3

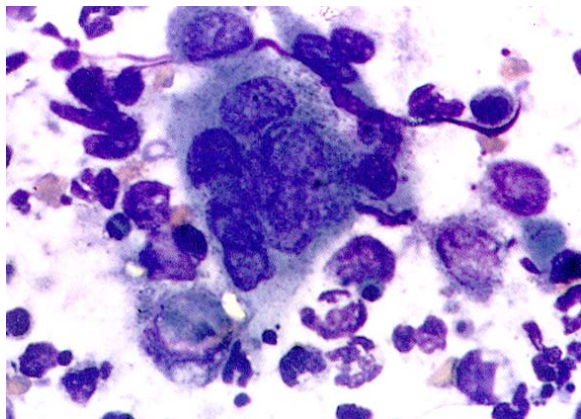


Figure 2



Figure 4